

2,5-DIMETHYL-4-PHENYL- AND 3,6-DIMETHYL-2,4-DIPHENYLPYPERIDINES

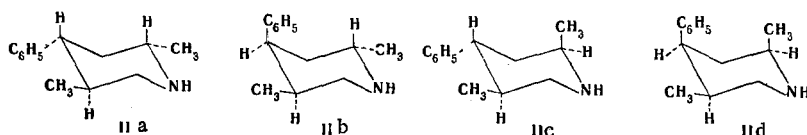
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2,5-Dimethyl-4-phenylpiperidine and 3,6-dimethyl-2,4-diphenylpiperidine were obtained by reduction of the corresponding substituted pyridines. Several of their transformations are examined.

The conversion of substituted pyridines to the corresponding piperidines results in the formation of several stereoisomeric forms of the latter. We selected 2,5-dimethyl-4-phenylpiperidine (II) and several of its derivatives as the objects of investigations in this respect. Piperidine II is close, in a stereochemical respect, to 1,2,5-trimethyl-4-phenyl-4-piperidol, which was isolated in the form of three diastereoisomers [1]. A study of the stereochemistry of II and compounds close to it makes it possible to extend our knowledge regarding the spatial structure of these piperidols and their derivatives and will make it possible to relate them synthetically and stereospecifically.

Four geometrical isomers of II are theoretically possible (their possible conversion forms are not indicated in the scheme).



Structures with equatorial phenyl groups are apparently more energetically favorable for isomer II_d and, possibly, for isomer II_b.

We have examined the reduction of 2,5-dimethyl-4-phenylpyridine (I) [2] by sodium in alcohol as well as the catalytic reduction in the presence of platinum. As one would have expected, a mixture of isomers (II) is formed by reduction of I with sodium in alcohol. Thin-layer chromatography indicated that II is a mixture of three stereoisomers: R_f 0.16, 0.32, and 0.78 [ether-methanol (2 : 1), aluminum oxide of activity IV], 0.67, 0.75, and 0.93 [ether-methanol (10 : 1), aluminum oxide of activity IV], 0.13, 0.47, and 0.81 [ether-methanol (2 : 1), aluminum oxide of activity II]. To a certain degree, the formation of a mixture of isomers was confirmed by a study of the picrates of II.

The band at 3290 cm^{-1} in the IR spectrum of II is attributed to the valence vibrations of the secondary amino group bonded with an intermolecular hydrogen bond. The band at 1670 cm^{-1} is attributed to the deformation vibrations of the same group. The spectrum does not contain a band at 880 cm^{-1} associated with nonplanar deformation vibrations of the C-H bonds of the pyridine ring.

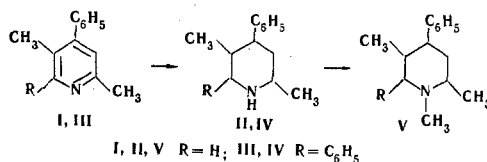
Only one of the isomers of II was isolated as a result of catalytic hydrogenation of I; this isomer differed in chromatographic characteristics from those indicated above. Thin-layer chromatography [(aluminum oxide of activities II and IV, ether-methanol (1 : 1), ether-methanol (2 : 1), methanol, heptane, methanol with added heptane, and heptane with added methanol] indicated the purity of the II obtained in this experiment - a single spot on the chromatogram in the ether-methanol (2 : 1) solvent system with R_f 0.092

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(Al_2O_3 with activity II). Comparison of the isolated picrates of II also indicates that the isomer obtained by catalytic hydrogenation of I differs from the isomers formed by reduction of I with sodium in alcohol. If one considers that cis addition of hydrogen occurs primarily during catalytic hydrogenation, the isomer obtained by catalytic hydrogenation can be assigned the IIc structure with cis positioning of the substituents at C_2 , C_4 , and C_5 . Three other isomers (IIa, b, c) are formed by reduction of I with sodium in alcohol. These considerations regarding the structure of II are, of course, hypothetical.

N-Methylation of a mixture of diastereoisomers II also resulted in the formation of a mixture of isomeric 1,2,5-trimethyl-4-phenylpiperidines (V). 3,6-Dimethyl-2,4-diphenylpiperidine (IV), which was isolated in the form of a single isomer, was obtained in 64% yield by reduction of 3,6-dimethyl-2,4-diphenylpyridine (III) [3] with sodium in alcohol.



1-Benzoyl-2,5-dimethyl-4-phenylpiperidine (VI) was obtained by Schotten-Baumann benzoylation of II. The band at 1640 cm^{-1} in the IR spectrum of VI is attributed to the stretching vibrations of the amide group.

EXPERIMENTAL

2,5-Dimethyl-4-phenylpiperidine (II). A. Sodium [60 g, 2.6 g-atom] was added to 20 g (0.109 mole) of I (bp $97\text{--}102^\circ/2\text{ mm}$, n_D^{20} 1.5828) in 400 ml of absolute alcohol. The mixture was heated for 3 h, after which 50 ml of water and 18% hydrochloric acid were added until an acid reaction to Congo Red was obtained. The alcohol was removed under a slight vacuum, and the residue was saturated with potassium hydroxide. The organic bases were extracted with ether. After distillation, 13.55 g (66%) of II with bp $114\text{--}115.5^\circ$ (3 mm) was obtained: n_D^{20} 1.5330, d_4^{20} 0.9749, MR_D 60.15, calc. 60.03. Found %: C 82.5; H 9.9. $\text{C}_{13}\text{H}_{19}\text{N}$. Calculated %: C 82.6; H 10.0.

Two crystal fractions were isolated on crystallization of the picrate of II: the first had mp $178\text{--}181^\circ$ (from alcohol); found %: N 13.1; the second had mp $165\text{--}167^\circ$ (from alcohol). Found %: N 13.4. $\text{C}_{13}\text{H}_{19}\text{N} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$. Calculated %: N 13.4.

B. A mixture of 6.77 g (0.031 mole) of the hydrochloride of I (mp $171\text{--}172^\circ$) in 40 ml of alcohol was dehydrogenated in the presence of 0.3 g of platinum oxide at room temperature. The calculated amount of hydrogen was absorbed in 12 days. The residue after removal of the catalyst and distillation of the alcohol was dissolved in water and saturated with potassium hydroxide. The organic bases were extracted with ether. After distillation in vacuo, 3.88 g (70%) of II with bp $118\text{--}119^\circ$ (3 mm) was isolated: n_D^{20} 1.5400, d_4^{20} 0.9900, MR_D 59.74, calc. 60.03. Found %: C 82.3; H 10.1. $\text{C}_{13}\text{H}_{19}\text{N}$. Calculated %: C 82.6; H 10.0.

The picrate of II had mp $161\text{--}162^\circ$ (from alcohol). Found %: N 13.3. $\text{C}_{13}\text{H}_{19}\text{N} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$. Calculated %: N 13.4. Mixing of a sample of this picrate with a sample of the picrate of II described above resulted in an appreciable melting point depression ($137\text{--}144^\circ$).

3,6-Dimethyl-2,4-diphenylpiperidine (IV). Compound IV with mp $127\text{--}128^\circ$ (from ethyl acetate) was obtained in 64.5% yield by similar reduction with sodium in alcohol of III. Found %: C 85.9; H 8.7; N 5.1. $\text{C}_{19}\text{H}_{23}\text{N}$. Calculated %: C 86.0; H 8.7; N 5.3. The picrate had mp $206\text{--}208^\circ$ (from alcohol). Found %: N 11.2. $\text{C}_{19}\text{H}_{23}\text{N} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$. Calculated %: N 11.3.

1,2,5-Trimethyl-4-phenylpiperidine (V). Formic acid [7.53 g (0.1 mole) of an 85% solution] was added dropwise to 7.73 g (0.041 mole) of II (obtained by reduction of I with sodium in alcohol) and 1.35 g (0.045 mole) of paraformaldehyde. The mixture was heated until evolution of carbon dioxide ceased, 40 ml of water was added, and the mixture was treated with sodium carbonate in the presence of ether to give 6.04 g (73%) of V with bp $105\text{--}106^\circ$ (1.5 mm): n_D^{20} 1.5235, d_4^{20} 0.9551, MR_D 64.97, calc. 64.99. Found %: C 82.8; H 10.4; N 6.7. $\text{C}_{14}\text{H}_{21}\text{N}$. Calculated %: C 82.7; H 10.3; N 6.9. The hydrobromide had mp $222.5\text{--}224^\circ$ (from acetone). Found %: N 4.6. $\text{C}_{14}\text{H}_{21}\text{N} \cdot \text{HBr}$. Calculated %: N 4.8.

Two picrate fractions were obtained from V. The first had mp 138–154° (from alcohol). Found %: N 12.6. The second had mp 200–202° (from alcohol). Found %: N 12.9. $C_{14}H_{21}N \cdot C_6H_3N_3O_7$. Calculated %: N 13.0.

1-Benzoyl-2,5-dimethyl-4-phenylpiperidine (VI). Benzoyl chloride [4.3 ml (0.037 mole)] was added dropwise with constant stirring to a mixture of 6.5 g (0.034 mole) of II (obtained by reduction of I with sodium in alcohol) and 8.75 ml (0.037 mole) of 20% potassium hydroxide. The reaction products were then extracted with ether. The ether solution was successively washed with potassium hydroxide, 10% sulfuric acid, and water. Compound VI [6.85 g (70%)] with bp 190–192° (2 mm) was obtained after drying with magnesium sulfate and distillation. Found %: N 4.7. $C_{20}H_{23}NO$. Calculated %: N 4.7.

The IR spectra were recorded with a UR-10 spectrophotometer from 3800–400 cm^{-1} with LiF, NaCl, and KBr prisms. The samples were prepared in the form of KBr tablets.

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